Signaling defects in iPSC-derived fragile X premutation neurons.

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Public Summary:
Fragile X-associated tremor/ataxia syndrome (FXTAS) is a leading monogenic, neurodegenerative disorder affecting premutation carriers of the fragile X (FMR1) gene. To investigate the underlying cellular neuropathology, we produced iPSC-derived neurons from isogenic subclones of primary fibroblasts of a female premutation carrier; with each subclone bearing exclusively either the normal or the expanded (premutation) form of the FMR1 gene as the active allele. We show that neurons harboring the stably-active, expanded allele (EX-Xa) have reduced PSD95 protein expression, reduced synaptic puncta density, and reduced neurite length. Importantly, such neurons are also functionally abnormal, with calcium transients of higher amplitude and increased frequency than for neurons harboring the normal-active allele. Moreover, sustained calcium elevation was found in the EX-Xa neurons after glutamate application. By excluding the individual genetic background variation, we have demonstrated neuronal phenotypes directly linked to the FMR1 premutation. Our approach represents a unique isogenic, X-chromosomal epigenetic model to aid the development of targeted therapeutics for FXTAS, and more broadly as a model for the study of common neurodevelopmental (e.g., autism) and neurodegenerative (e.g., Parkinsonism; dementias) disorders.

Scientific Abstract:
Fragile X-associated tremor/ataxia syndrome (FXTAS) is a leading monogenic, neurodegenerative disorder affecting premutation carriers of the fragile X (FMR1) gene. To investigate the underlying cellular neuropathology, we produced iPSC-derived neurons from isogenic subclones of primary fibroblasts of a female premutation carrier; with each subclone bearing exclusively either the normal or the expanded (premutation) form of the FMR1 gene as the active allele. We show that neurons harboring the stably-active, expanded allele (EX-Xa) have reduced PSD95 protein expression, reduced synaptic puncta density, and reduced neurite length. Importantly, such neurons are also functionally abnormal, with calcium transients of higher amplitude and increased frequency than for neurons harboring the normal-active allele. Moreover, sustained calcium elevation was found in the EX-Xa neurons after glutamate application. By excluding the individual genetic background variation, we have demonstrated neuronal phenotypes directly linked to the FMR1 premutation. Our approach represents a unique isogenic, X-chromosomal epigenetic model to aid the development of targeted therapeutics for FXTAS, and more broadly as a model for the study of common neurodevelopmental (e.g., autism) and neurodegenerative (e.g., Parkinsonism; dementias) disorders.